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(54) Title: A PROCESS FOR THE MICROENCAPSULATION OF MEDICAMENTS

(57) Abstract

A process for the microencapsulation of a medicament by means of at least one coating agent, which comprises the following steps: a) Mixing the medicament with the coating agent; b) Heating the mixture, kept under strong stirring, to cause the only coating agent to melt; c) Keeping the mixture under stirring at the coating agent melting temperature; d) Cooling the mixture with constant stirring; e) Recovering the microcapsules.

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A PROCESS FOR THE MICROENCAPSULATION OF MEDICAMENTS

The present invention relates to a microencapsulation for masking the unpleasant bitter taste of water-insoluble medicaments by means of one or more water-insoluble substances having melting point lower than the melting point of the medicament to be microencapsulated, and to the pharmaceutical compositions containing said microencapsulated medicaments.

The present invention relates to pharmaceutical preparations, more specifically tablets, chewable tablets, suspensions mainly in aqueous carrier and in general oral pharmaceutical forms containing a medicament in the form of microcapsules, the process for the preparation of microencapsulated medicaments, the pharmaceutical formulations prepared starting from said medicaments and the methods for the preparation thereof.

In the following, "medicament" means a therapeutically active, organic or inorganic compound, whereas "microencapsulated medicament" relates to a medicament particle or particles aggregates, of varying thickness, coated with one or more organic filmogenic agents, sparingly water-soluble and free from taste.

"Conventional pharmaceutical excipients" means all the excipients used for the formulation of pharmaceutical forms, such as ligands, suspending agents, sweetening agents, flavours, stabilizing agents, dyes, wetting agents and the like.

"Coating agent" means one or more organic, natural or synthetic, non toxic, free from taste, substances conventionally used for the preparation of pharmaceutical formulations.

Microencapsulation is a relatively recent technology

which allows to coat particles of solids or small drops of liquids, in single form or as aggregates, with substances having polymeric structure thereby obtaining microcapsules having a size of about 0.1-1000 micron.

Microencapsulation techniques mainly used can be grouped in three classes:

- processes utilizing phase separation;
- processes based on interface polymerization;
- physical processes, such as centrifugation, extrusion and the like.

In practice, most microencapsulation procedures make use of the phase separation technique. Examples are disclosed in: EP 212,751, US 4,766,012, EP 413,533, US 4,460,563, US 4,462,982, US 4,835,187.

Physical processes are generally not very used in that they provide unsatisfactory microcapsules with hardly reproducible results.

The present invention makes use of a physical process combined with a highly efficient mechanical action capable of overcoming the drawbacks mentioned above.

The process of the invention is based on the capability of a hydrophobic substance, when heated above its melting point, of homogeneously distributing as a thin layer on medicament crystals or crystal aggregates kept in strong motion; the subsequent cooling causes the coating agent to solidify around the particle or particle aggregates, thus resulting in microcapsules free from taste and odour.

The present invention therefore provides a process for the microencapsulation of a medicament by means of at least one coating agent, which comprises the following steps:

a) Mixing the medicament with the coating agent;
b) Heating the mixture, kept under strong stirring, to cause the only coating agent to melt;

c) Keeping the mixture under stirring at the coating agent melting temperature;

d) Cooling the mixture with constant stirring;

e) Recovering the microcapsules.

For the preparation of the microcapsules according to the present invention, the amount of coating for use compared with the medicament should range between 1 and 50%, preferably between 2.5 and 25%, more preferably between 5 and 20%.

The coating agents can be selected from water-insoluble substances, generally of lipid nature, pharmaceutically acceptable and with melting point lower than the medicament to be microencapsulated.

Examples of coating agents comprise:

Long chain aliphatic alcohols such as: cetyl alcohol m.p. 49°C, myristyl alcohol m.p. 38°C, stearyl alcohol m.p. 59.4-59.8°C.

Long chain aliphatic acids: such as stearic acid m.p. 69-70°C, palmitic acid m.p. 63-64°C, myristic acid m.p. 58.5°C, lauric acid m.p. 44-48°C, arachidic acid m.p. 75.5°C, etc.

Esters of fatty acids and aliphatic alcohols: methyl arachidate m.p. 47°C, ethyl arachidate m.p. 41°C, methyl stearate m.p. 38-39°C, ethyl stearate m.p. 33-35°C, glyceryl monostearate m.p. 56-58°C, glyceryl tripalmitate m.p. 66°C, glyceryl behenate (compritol), glyceryl palmitostearate (precirolate), lauroyl macrogol 32 glyceride (gelucire 44/14) stearoyl macrogol 32 glyceride (gelucire 50/13), castor oil.

The medicament can be mixed with the coating agent in horizontal or vertical working mixer granulators equipped with high shear mixing paddles, high efficiency crushers and heating and cooling jackets; this type of devices are

commercially available under the trade marks Diosna, Collette, Zanchetta, Lödige.

The medicaments which can be used according to the invention should be insoluble both in the selected coating agent and in water, in case aqueous formulations have to be prepared. Moreover, the melting point of the medicaments should be markedly higher than the melting point of the coating agent.

Examples of medicaments which can conveniently be formulated according to the process of the invention comprise:

nonsteroidal anti-inflammatory drugs:
ibuprofen, flurbiprofen, diclofenac, ketoprofen, naproxen, flufenamic acid, paracetamol, nimesulide, lornoxicam, indoprofen, indomethacin, ibufenac, etodolac, diflunisal, carbamazepine, bromfenac, aceclofenac, acetylsalicylic acid, codeine base, morphine base, tenoxicam, propyphenazon, ketorolac or the salts thereof;

antibiotics: ampicillin, amoxicillin, cephalexin, erythromycin and derivatives, fosfomycin, miocamycin, rokitamycin,roxitromycin, or the salts thereof;

antitussives: dextromethorphan hydrobromide, noscapine;

antihistamines: oxatomide;

antiulcers: cimetidine, famotidine, ranitidine, sucralfate;

mucolytics: bromhexine.

Nonsteroidal antiinflammatories, in particular arylpropionic acids such as Ibuprofen, ketoprofen, naproxen, as well as antihistamines, such as oxatomide, are preferred.

Said active ingredients, particularly ibuprofen, encapsulated according to the invention, have substantially the same bioavailability as the non-microencapsulated drug.

The invention is described in greater detail in the following examples:

Example 1

Suspension containing Ibuprofen

Quali-quantitative composition for 100 ml of suspension:

Ibuprofen	2.000 g
Cetyl alcohol	0.200 g
Saccharose	50.000 g
Saccharose palmitostearate	0.500 g
Methyl p-hydroxybenzoate	0.100 g
Propyl p-hydroxybenzoate	0.020 g
Dimethicone (10% emulsion)	0.500 g
Aluminium magnesium silicate	2.300 g
Caramel-toffee flavour	0.200 g
Purified water q.s. to	100.000 ml

Preparation procedure:

- Preparation of the microcapsules

The necessary amount of Ibuprofen and cetyl alcohol is placed in a mixer granulator, mixing for about 10 minutes in the following conditions:

mixing paddle: 15-20 r.p.m.

crusher: 3000 r.p.m.

The stirred mass is heated by circulating hot water in the Diosna jacket, preventing the temperature of the product from exceeding 55°C. Once reached this temperature, stirring is continued for about 5 minutes, then cooling is started at a rate of about 1-2° per minute.

After reaching room temperature, the Ibuprofen microcapsules are unloaded and sieved through 0.5 mm, 0.25 mm and 0.10 mm sieves.

- Preparation of the suspension

In a stainless steel container of suitable capacity, equipped with screw stirrer, almost all of the necessary water is loaded, and saccharose and preservatives are dissolved therein; solubilization has to be carried out at

about 60-70°C. After cooling to room temperature (25°C), the syrup is added, in succession, with saccharose palmitostearate and the Ibuprofen microcapsules.

The whole is stirred to obtain a homogeneous suspension, then dimethicone, magnesium-aluminium silicate, flavour and the remaining amount of purified water are added. The suspension is kept under strong stirring for about 10 minutes, then it can be distributed in ampoules.

In vitro bioavailability tests were carried out with Ibuprofen microcapsules compared with non-microencapsulated Ibuprofen for evaluating the how the cetyl alcohol amount affects the active ingredient release rate.

The procedure used is the same as reported in European Pharmacopoeia for Ibuprofen tablets;

Apparatus: type II

Dissolution medium: Phosphate Buffer pH = 7.2

Temperatures: 37°C ± 0.5°C

Rotation Speed: 100 rpm

The resulting diagram is reported in figure 1.

Example 2

Suspension containing acid diclofenac.

Quali-quantitative composition for 100 ml of suspension:

Diclofenac acid	0.500 g
Cetyl alcohol	0.075 g
Saccharose	50.000 g
Saccharose palmitostearate	0.500 g
Sodium Benzoate	0.500 g
Dimethicone (10% emulsion)	0.500 g
Aluminium magnesium silicate	2.300 g
Tropical Flavour	0.200 g
Purified water	q.s. to 100.000 ml

Preparation procedure:

The same procedure as in example 1 is followed.

Example 3

Suspension containing on Naproxen

Quali-quantitative composition for 100 ml of suspension:

Naproxen		2.500 g
Compritol		0.250 g
Saccharose		50.000 g
Saccharose palmitostearate		0.500 g
Sodium Benzoate		0.500 g
Dimethicone (10% emulsion)		0.500 g
Aluminium magnesium silicate		2.300 g
Caramel flavour		0.200 g
Purified water	q.s. to	100.000 ml

Preparation procedure:

The same procedure as in Example 1 is followed, the only changed parameter being the temperature in the microencapsulation step; in this case the temperature of the mass has to be raised to 85°C.

Example 4

Suspension containing Ketoprofen

Quali-quantitative composition for 100 ml of suspension:

Ketoprofen		0.500 g
Compritol		0.050 g
Saccharose		50.000 g
Saccharose palmitostearate		0.500 g
Methyl p-hydroxybenzoate		0.100 g
Propyl p-hydroxybenzoate		0.020 g
Dimethicone (10% emulsion)		0.500 g
Aluminium magnesium silicate		2.300 g
Orange flavour		0.200 g
Purified water	q.s. to	100.000ml

Preparation procedure:

The same procedure as in Example 1 is followed, the only changed parameter being the temperature in the

microencapsulation step; in this case the temperature of the mass has to be raised to 85°C.

Example 5

Chewable tablets containing Oxatomide

Quali-quantitative composition for a chewable tablet:

Oxatomide	0.015 g
Compritol	0.002 g
Lactose	0.263 g
Sorbitol	0.400 g
Mannitol	0.200 g
Aspartame	0.050 g
Orange flavour	0.060 g
Magnesium stearate	0.010 g

Preparation procedure:

The same procedure as in Example 1 is followed.

Tablets are prepared according to the conventional water-humid granulation technology, the granulate being dried and mixed with flavours and sweetening agents, then pressed to the desired weight.

Example 6

Chewing-gum containing Oxatomide

Quali-quantitative unitary composition:

Oxatomide	7.500 mg
Compritol	1.000 mg
Sorbitol	0.800 g
Mannitol	0.300 g
Isomalt	0.060 g
Maltitol	0.100 g
Mint flavour	0.020 g
Glicamil	0.025 g
Powder propolis	0.025 g
Titanium dioxide	0.005 g

Base gum 0.320 g

Preparation procedure:

The same procedure as in Example 1 is followed.

The chewing-gum is prepared according to the conventional technology.

Example 7

Oral suspension containing 2%, 4%, 6% Ibuprofen.

Quali-quantitative composition for 100 ml of suspension:

COMPONENTS	2% Suspen.	4% Suspen.	6% Suspen.
Ibuprofen	2.000 g	4.000 g	6.000 g
Cetyl alcohol	0.223 g	0.446 g	0.669 g
Saccharose	60.000 g	60.000 g	60.000 g
Saccharose palmitostearate	0.500 g	0.500 g	0.500 g
Methyl p-hydroxy-benzoate	0.100 g	0.100 g	0.100 g
Propyl p-hydroxy-benzoate	0.020 g	0.020 g	0.020 g
EDTA sodium salt	0.100 g	0.100 g	0.100 g
Citric acid	0.200 g	0.200 g	0.200 g
Kaolin	1.000 g	1.000 g	1.000 g
Dimethicone	0.050 g	0.050 g	0.050 g
Xanthan gum	0.500 g	0.500 g	0.600 g
Banana flavour	0.150 g	0.200 g	0.300 g
Honey flavour	0.050 g	0.100 g	0.150 g
Purified water q.s. to	100 ml	100 ml	100 ml

Preparation procedure:

The same procedure as in Example 1 is followed.

Preparation of the suspension: as described in Example 1.

The in vivo bioavailability of the formulation containing 2% Ibuprofen was compared with that of a similar

commercial formulation.

Annexed figure 2 shows the plasma concentrations obtained after administration of a dose of suspension equivalent to 200 mg Ibuprofen (reference Ibuprofen; micro-encapsulated Ibuprofen suspension).

The areas under each plasma concentration should be considered completely equivalent in that their ratio lies within the range 0.8-1.25 (calculated value 1.11).

The obtained results prove that the microencapsulation of Ibuprofen does not significantly affect bioavailability.

Example 8

Oral suspension containing 2%, 4%, 6% Naproxen.

Quali-quantitative composition for 100 ml of suspension

COMPONENTS	2%. Suspen	4% Suspen.	6% Suspen.
Naproxen (acid form)	2.000 g	4.000 g	6.000 g
Cetyl alcohol	0.223 g	0.446 g	0.669 g
Saccharose	60.000 g	60.000 g	60.000 g
Saccharose palmitostearate	0.500 g	0.500 g	0.500 g
Methyl p-hydroxy benzoate	0.100 g	0.100 g	0.100 g
Propyl p-hydroxy-benzoate	0.020 g	0.020 g	0.020 g
EDTA sodium salt	0.100 g	0.100 g	0.100 g
Citric acid	0.200 g	0.200 g	0.200 g
Kaolin	1.000 g	1.000 g	1.000 g
Dimethicone	0.050 g	0.050 g	0.050 g
Xanthan gum	0.500 g	0.500 g	0.600 g
Banana flavour	0.150 g	0.200 g	0.300 g
Honey flavour	0.050 g	0.100 g	0.150 g
Purified water q.s. to	100 ml	100 ml	100 ml

Preparation procedure:

The same procedure as in Example 1 is followed.

Preparation of the suspension: as described in Example 1.

Example 9

Oral suspension containing 0.5%, 1%, 5% Diclofenac

Quali-quantitative composition for 100 ml of suspension

COMPONENTS	0.5% Suspen.	1% Suspen.	5% Suspen.
Diclofenac (acid form)	0.500 g	1.000 g	5.000 g
Cetyl alcohol	0.075 g	0.150 g	0.750 g
Saccharose	60.000 g	60.000 g	60.000 g
Saccharose palmitostearate	0.500 g	0.500 g	0.500 g
Methyl p-hydroxy benzoate	0.100 g	0.100 g	0.100 g
Propyl p-hydroxy-benzoate	0.020 g	0.020 g	0.020 g
EDTA sodium salt	0.100 g	0.100 g	0.100 g
Citric acid	0.200 g	0.200 g	0.200 g
Kaolin	1.000 g	1.000 g	1.000 g
Dimethicone	0.050 g	0.050 g	0.050 g
Xanthan gum	0.500 g	0.500 g	0.500 g
Banana flavour	0.150 g	0.200 g	0.200 g
Honey flavour	0.050 g	0.100 g	0.200 g
Purified water q.s. to	100 ml	100 ml	100 ml

Preparation procedure:

The same procedure as in Example 1 is followed.

Preparation of the suspension: as described in example 1.

Example 10

Sugar-free oral suspension containing 2% Ibuprofen

Quali-quantitative composition for 100 ml of suspension:

COMPONENTS	0.5% Suspen.
Ibuprofen	2.000 g
Cetyl alcohol	0.223 g
Maltitol (70% sol.)	60.000 g
Saccharose palmitostearate	0.500 g
Domifen bromide	0.010 g
Sodium saccharin	0.100 g
EDTA sodium salt	0.100 g
Citric acid	0.200 g
Kaolin	1.000 g
Dimethicone	0.050 g
Xanthan gum	0.500 g
Flavour	0.300 g
Purified water q.s. to	100 ml

Preparation procedure:

The same procedure as in Example 1 is followed.

Preparation of the suspension: as described in example 1.

CLAIMS

1. A process for the microencapsulation of a medicament by means of at least one coating agent, which comprises the following steps:

a) Mixing the medicament with the coating agent;

b) Heating the mixture, kept under strong stirring, to cause the only coating agent to melt;

c) keeping the mixture under stirring at the melting temperature of the coating agent;

d) Cooling the mixture with constant stirring;

e) Recovering the microcapsules.

2. A process as claimed in claim 1 wherein the coating agent is selected from long chain aliphatic alcohols, long chain aliphatic acids, esters of fatty acids with aliphatic alcohols.

3. A process as claimed in claim 1 or 2 in which the medicament is a non-steroidal antiinflammatory - analgesic agent.

4. A process as claimed in claim 3 in which the medicament is an arylpropionic acid or a salt thereof or an antihistamine.

5. A process as claimed in claim 4 in which the medicament is ibuprofen, ketoprofen or naproxen.

6. A process as claimed in claim 4 in which the medicament is anhydrous or hydrated oxatomide.

7. Microcapsules obtainable with the process of claims 1-6.

8. Oral pharmaceutical compositions containing the microcapsules of claim 7.

9. Compositions according to claim 8, comprising as the active ingredient ibuprofen, ketoprofen, naproxen or oxatomide, said drugs having substantially the same

bioavailability as the corresponding non-encapsulated drug.

10. Pharmaceutical compositions as claimed in claim 8 or 9 in the form of tablets, chewable tablets, chewing-gums, suspensions.

FIGURE 1

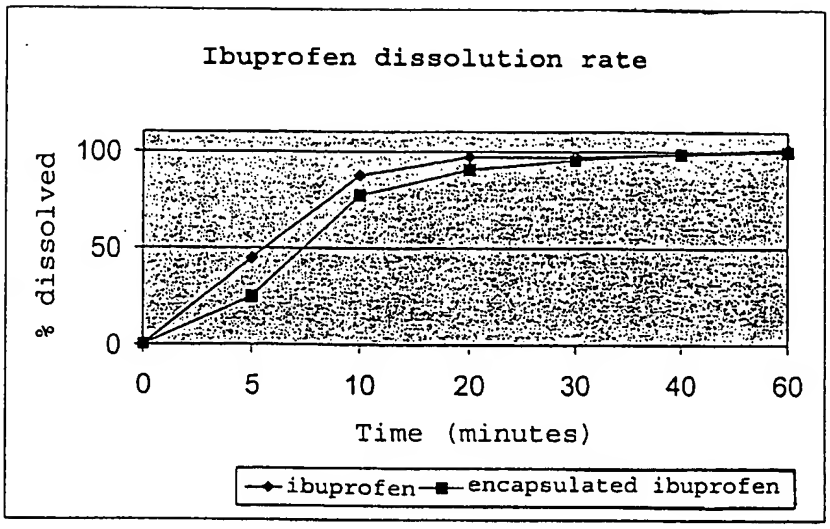
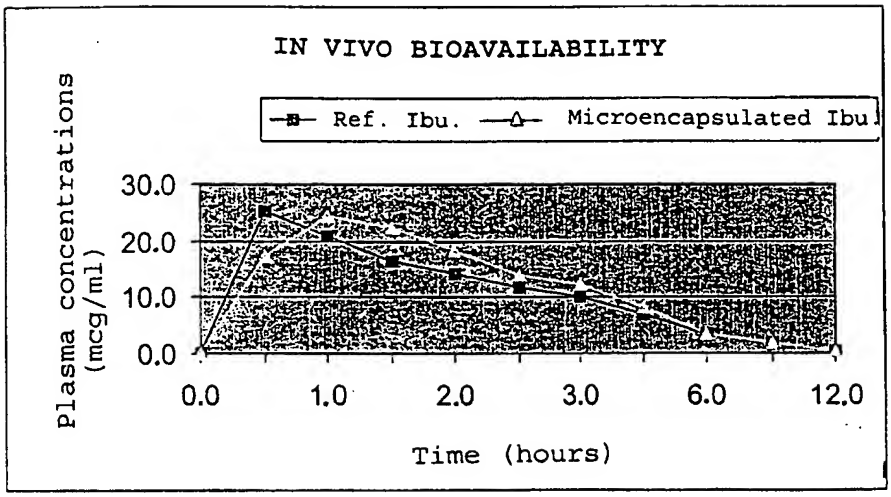

Ibuprofen dissolution rate
% dissolved
100
50
0
0
5
10
20
30
40
60
Time (minutes)
ibuprofen
encapsulated ibuprofen

Figure 2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Ref. Ibu.
Microencapsulated Ibu.
Plasma concentrations (mcg/ml)
30.0
20.0
10.0
0.0
0.0
1.0
2.0
3.0
6.0
12.0
Time (hours)